

PATENT COOPERATION TREATY

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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 05 February 1998 (05.02.98)	Applicant's or agent's file reference IS/CP5627310
International application No. PCT/GB97/01819	Priority date (day/month/year) 05 July 1996 (05.07.96)
International filing date (day/month/year) 04 July 1997 (04.07.97)	
Applicant LEADLAY, Peter, Francis et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
19 January 1998 (19.01.98)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Nicola Wolff
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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference IS/CP5627310	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)	
International application No. PCT/GB97/01819	International filing date (day/month/year) 04/07/1997	Priority date (day/month/year) 05/07/1996
International Patent Classification (IPC) or national classification and IPC C12N15/00		
Applicant BIOTICA TECHNOLOGY LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 19/01/1998	Date of completion of this report 19. 10. 98
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Hardon, E Telephone No. (+49-89) 2399-8414 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB97/01819

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-132 as originally filed

Claims, No.:

1-23 as originally filed

Drawings, sheets:

1-32 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☒ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB97/01819

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
- ☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
- ☒ all parts.
- ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-14, 20-23
	No:	Claims	1, 15-19
Inventive step (IS)	Yes:	Claims	13
	No:	Claims	1-12, 14-23
Industrial applicability (IA)	Yes:	Claims	1-23
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB97/01819

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB97/01819

1. Unity of invention.

1.1. The international search authority (ISA) found that the present claims lack unity.

Two potential inventions were identified:

(1) A hybrid polyketide synthetase (PKS) gene comprising portions of the coding regions of two different type I PKS, hybrid PKS encoded thereby, vector and transformed organism containing said gene, method of producing the organism, use of the organism for making a PK and the PK so obtained (claims 1-19).

(2) Use of a type II PKS promoter to control a heterologous gene and nucleic acid comprising said promoter operably linked to a heterologous gene (claims 20-23).

In response to an invitation from the ISA the applicant paid an additional search fees and both potential inventions have been searched.

1.2. The international examination authority agrees with the objection for lack of unity raised by the search authority. The only technical feature common to the above indicated (groups of) potential inventions is that they are concerned with PKS genes. As indicated by the ISA the two classes of PKS were state of the art. Genes (gene clusters) encoding both class I and class II PKS, including the promoters, were available and had been the subject of genetic manipulation (e.g. Cortes et al., WO95/08548). The underlying technical problem for these groups of potential invention is also different: obtaining novel polyketides for invention 1 and obtaining efficient expression of a heterologous coding sequence for invention 2. Thus no special technical feature(s) can be seen which could provide a common inventive concept for the claimed inventions.

Note that a further objection for lack of unity can be raised against the matter of claims 1-19 since the unifying concept linking this matter, i.e. domain shuffling in PKS type I genes, is found to lack novelty (see point 4.1. herein below).

This objection has, however, not been pursued at this stage of the procedure.

In response to an invitation from the international examination authority the applicant paid an additional examination fee and both potential inventions have been examined.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB97/01819

Priority.

2. The first claimed priority is presumed to be valid for the entire claimed matter. If not, the P/X documents mentioned in the search report could be detrimental to the novelty and/or inventive activity of the matter of present claims 1 to 19.

Clarity.

3. The present claims contain a number of unclarities.
- (i) In claim 1 it is not clear whether the polyketide synthases (PKS) already qualify as "heterologous" when they are derived from two different genes (e.g. a DEBS1/DEBS2 hybrid) or whether they need to be from different organisms.
 - (ii) In claim 2 the term "loading module" is used. In claim 3 this loading module is further characterised as consisting of an AT and ACP activity. It is not clear what other loading modules could be embraced in claim 2. Claim 3 would thus appear redundant.
 - (ii) The use of the ill-defined term "combinatorial modules" renders the scope of claim 8 unclear.
 - (iv) In claim 19 a PK is characterised solely as the product of the hybrid PKS of the preceding claims. This feature does not, however, in any way define the PK itself. The scope of said claim is thus unclear.
4. Novelty and inventive step of potential invention I.
- 4.1. (i) Cortes et al. (D3; document numbering corresponds to the order of citation in the search report) is a document citing the present inventors among the authors. It discloses a hybrid DEBS1/DEBS3 construct which is considered to fall within the terms of claim 1.
- (ii) Oliynyk et al. (D8) is another document citing the present inventors among the authors. It describes the replacement of the AT domain from module 1 of DEBS1-TE by the AT domain of module 2 of rapamycin. It is reported that a novel compound was obtained in good yield. This document is thus detrimental to the novelty of present claim 1 and also claims 15 to 19. For claim 19 it should furthermore be noted that a hybrid PKS does not necessarily produce a novel PK.
- (iii) A large number of "mix and match" experiments exchanging functional units of class II PKS have been done; see e.g. Kosla et al. (D7). This has in some cases allowed the efficient synthesis of novel compounds. In D3 and D8 the present inventors successfully extend these experiments to a class I PKS. D3 and

D8, in particular D8, thus clearly establish the possibility of domain swaps in type I PKS (see conclusions of D8). These documents are therefore considered detrimental to the inventive activity of present claims 2 to 12 and 14 which are concerned with mere technical details of possible domain exchanges.

Novelty and inventive step of potential invention II.

- 4.2. (i) Several PKS type II promoters were known in the art; see e.g. Parro et al. (D2) for act I and the documents cited by the applicant on page 128 of the description for other such promoters. Present claims 20 to 23 embrace even trivial reporter gene (e.g. CAT) constructs with these promoters and their use for analysing the promoters. Analysing the structure and regulation of a known promoter with the use of a reporter gene is the logical next step after the identification of a promoter. Claim 20 to 23 therefore lack an inventive step over the above indicated documents.
- (ii) It could, however, not be foreseen that the act I promoter of *S. coelicolor* accompanied by its natural activator gene would be favourable for the expression of type I PKS at least in certain host cells. An inventive step is thus recognised for claim 13.

Sufficiency of potential invention II.

5. Claims 20 to 22 are not limited to the specific act I regulatory unit which was shown to have favourable properties, at least in a *Saccharopolyspora erythraea* host, but embrace any type II PKS promoter. It is unlikely that these favourable properties are shared by all other PKS type II promoters. To determine which of the other type II PKS promoters, if any, has comparable favourable properties would require undue experimentation. The matter of claims 20 to 22 insofar as these other promoters are concerned is thus considered insufficiently disclosed.

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference IS/CP5627310	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 97/ 01819	International filing date (day/month/year) 04/07/1997	(Earliest) Priority Date (day/month/year) 05/07/1996
Applicant BIOTICA TECHNOLOGY LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (see Box I).

2. ☒ Unity of invention is lacking (see Box II).

3. ☒ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing

☐ filed with the international application.

☒ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the title, ☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

Figure No. 2A ☐ as suggested by the applicant.

☐ None of the figures.

☒ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 97/01819

B x I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

1. Claims: 1-19

Hybrid polyketide synthase gene, hybrid polyketide synthase thereby encoded, vector and transformed organism containing said gene, method of producing such a transformed organism, use thereof for making a polyketide and polyketide so obtained.

2. Claims: 20-23

Use of a type II PKS promoter to control a heterologous gene and nucleic acid comprising a type II PKS promoter operably linked to a heterologous gene

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/01819

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/52 C12N15/62 C12N9/00 C12N15/81 C12N1/19
C12P19/62

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C12P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 95 08548 A (LELAND STNAFORD JUNIOR UNIVERSITY) 30 March 1995 see page 5, line 1 - page 7, line 12 see page 15, line 21 - page 16, line 32 see page 23, line 22 - page 26, line 15 see page 27, line 12 - page 28, line 2 see page 29, paragraph 1 see page 30, paragraph 2 - page 31, paragraph 1 see page 43, line 25 - page 45, line 4 --- -/--</p>	1,3,8, 14-23

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

18 February 1998

Date of mailing of the international search report

03-03-1998

Name and mailing address of the ISA

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Authorized officer

Gurdjian, D

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>PARRO, VICTOR ET AL: "Transcription of genes involved in the earliest steps of actinorhodin biosynthesis in Streptomyces coelicolor"</p> <p>NUCLEIC ACIDS RES. (1991), 19(10), 2623-7</p> <p>CODEN: NARHAD;ISSN: 0305-1048, XP002056140</p> <p>see abstract</p> <p>see page 2626, right-hand column, paragraph 2 - page 2627, paragraph 3</p> <p>---</p>	20-22
A	<p>JESUS CORTES ET AL.: "Repositioning of a domain in a modular polyketide synthase to promote specific chain cleavage"</p> <p>SCIENCE,</p> <p>vol. 268, no. 5216, 9 June 1995,</p> <p>LANCASTER, PA US,</p> <p>pages 1487-1489, XP002045167</p> <p>cited in the application</p> <p>see abstract</p> <p>see page 1487, right-hand column, paragraph 2 - page 1489, left-hand column, last paragraph</p> <p>---</p>	1-19
A	<p>STEFANO DONADIO ET AL.: "An erythromycin analog produced by reprogramming of polyketide synthesis"</p> <p>PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,</p> <p>vol. 90, no. 15, 1 August 1993, WASHINGTON US,</p> <p>pages 7119-7123, XP002045168</p> <p>cited in the application</p> <p>see abstract</p> <p>see page 7119, right-hand column, paragraph 2</p> <p>see page 7120, right-hand column, paragraph 2; figure 2</p> <p>see page 7122, right-hand column, paragraph 2 - page 7123, left-hand column, last paragraph</p> <p>---</p>	1-19
A	<p>WO 93 13663 A (ABBOTT LABORATORIES) 22 July 1993</p> <p>cited in the application</p> <p>see page 2, line 17 - page 3, line 2</p> <p>see page 6, line 1 - page 9, line 25</p> <p>---</p>	1-19
A	<p>MCDANIEL R ET AL: "CONSTRUCTION OF HYBRID POLYKETIDE SYNTHASES VIA GENE REPLACEMENTS AND ANALYSIS OF POLYKETIDE PRODUCTS."</p> <p>205TH ACS (AMERICAN CHEMICAL SOCIETY) NATIONAL MEETING, DENVER, COLORADO, USA, MARCH 28-APRIL 2, 1993. ABSTR PAP AM CHEM SOC 205 (1-2). 1993. BIOT 12. CODEN: ACSRAL ISSN: 0065-7727, XP002045169</p> <p>---</p> <p>-/--</p>	1-19

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KHOSLA, CHAITAN ET AL: "Genetic construction and functional analysis of hybrid polyketide synthases containing heterologous acyl carrier proteins" J. BACTERIOL. (1993), 175(8), 2197-204 CODEN: JOBAAY;ISSN: 0021-9193, 1993, XP002045170 ---	1-19
A	OLIYNYK, MARKIYAN ET AL: "A hybrid modular polyketide synthase obtained by domain swapping" CHEM. BIOL. (1996), 3(10), 833-839 CODEN: CBOLE2;ISSN: 1074-5521, 1996, XP002045171 see page 833, right-hand column, paragraph 2 - page 837, right-hand column, paragraph 2 ---	1-19
A	FERNANDEZ-MORENO M A ET AL: "NUCLEOTIDE SEQUENCE AND DEDUCED FUNCTIONS OF A SET OF COTRANSCRIBED GENES OF STREPTOMYCES COELICOLOR A3(2) INCLUDING THE POLYKETIDE SYNTHASE FOR THE ANTIBIOTIC ACTINORHODIN" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 267, no. 27, 25 September 1992, pages 19278-19290, XP000652285 see the whole document ---	1-23
P,X	KUHSTOSS S ET AL: "Production of a novel polyketide through the construction of a hybrid polyketide synthase" GENE, vol. 183, no. 1, December 1996, page 231-236 XP004062752 see abstract see page 233, left-hand column, paragraph 1 - page 235, left-hand column, paragraph 2 ---	1-5, 14-19
P,X	WO 96 40968 A (UNIV LELAND STANFORD JUNIOR ;JOHN INNES CENTRE (GB)) 19 December 1996 see page 5, line 5 - page 9, line 3 see page 18, line 16 - page 22, line 6 see page 25, line 24 - page 29, line 8 see page 37, line 3 - line 35 see page 38, line 10 - page 39, line 24 see page 51, line 9 - page 52, line 4; examples -----	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

Information on application No

PCT/GB97/01819

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9508548 A	30-03-95	US 5672491 A	30-09-97
		AU 678058 B	15-05-97
		AU 7731794 A	10-04-95
		CA 2171629 A	30-03-95
		EP 0725778 A	14-08-96
		JP 9505983 T	17-06-97
		US 5712146 A	27-01-98

WO 9313663 A	22-07-93	CA 2100791 A	18-07-93
		AU 665526 B	11-01-96
		AU 1245092 A	03-08-93
		EP 0626806 A	07-12-94

WO 9640968 A	19-12-96	US 5712146 A	27-01-98
		AU 6157596 A	30-12-96
